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Case Report

The sudden and unexpected death of a female-to-male transsexual patient

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Abstract

A 32-year-old woman, who was intramuscularly injected with testosterone enanthate (125 mg) once or twice a month over a two-year period for female-to-male transsexualism, died suddenly. A forensic autopsy was performed to investigate the cause of death. Concentric cardiac hypertrophy was macroscopically observed. In the left and right coronary arteries, atherosclerosis was generally observed within the endothelium. In particular, there was severe stenosis (>90%) at the start of the left descending branch. In the myocardium, both coagulation necrosis and contraction band necrosis were microscopically observed. Moreover, myocardial fibrosis and myocardial calcification were diffusely detected, respectively. The cause of death was diagnosed as ischemic heart disease due to coronary stenosis. There is some debate as to whether cross-hormone replacement is related to the occurrence of coronary artery disease or not, however, it is possible that the development of ischemic heart disease was aggravated by the administration of testosterone enanthate in the current case.

Keywords: Female-to-male; Transsexualism; Testosterone; Sudden death; Ischemic heart disease

1. Introduction

Transsexualism was initially defined at the beginning of the 1960's as biological normality associated with a feeling of belonging to the opposite sex rather than to one's own gender resulting in a request for sex reassignment.[1,2] On the basis of reports from various countries, the prevalence of transsexual people has been estimated to be as high as 1 in 30 000 males and 1 in 100 000 females.[2,3]

We describe an autopsy case of the sudden and unexpected death of a young female-to-male transsexual patient, who had been treated with cross-sex hormone replacement. In this article, we discuss the relationship between the cause of death and cross-sex hormonal treatment on the basis of macro- and micro-scopic autopsy findings, her clinical history and hormonal determinations of androgen, estrogen and the other hormones in the post-mortem blood.

2. Case report

A 32-year-old female, who was a female-to-male transsexual person, complained of chest pain, and then suddenly

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lost consciousness. She was carried to an emergency hospital and cardiopulmonary resuscitation was performed, however, she died without the recovery of her heartbeat. In accordance with a criminal investigation, the detailed history of her transsexualism was not known, however, she had changed her name to that of a man two years prior to her death. Moreover, androgenic hormone (testosterone enanthate, 125 mg) had been intramuscularly injected once or twice a month by an obstetrician for at least two years before her death, and the latest injection of the hormone had been one week before her death. Several months before her death, she had felt chest discomfort; nevertheless, further examinations of this symptom were not undertaken. Two days before her death, she was easily diagnosed as suffering from reflux esophagitis by a local physician because of chest discomfort, but there were no significant findings on gastrointestinal endoscopic examination the following next day. To investigate the cause of death, a forensic autopsy was performed at Kyushu University.

2.1. Autopsy findings

On external examination, the deceased, who had strong muscles, was 154 cm tall and weighed 53 kg. There was strong post-mortem lividity on the back. There was no significant injury with the exception of a contused small wound and subcutaneous hemorrhage on the left upper eyelid, and small abrasions and small subcutaneous hemorrhage on the bilateral hands. Acne was observed on her face. Hirsutism appeared on her external genitalia, however, hypertrophy of the clitoris was not observed. The heart weighed 309 g. Concentric myocardial hypertrophy was seen in the left ventricle (Fig. 1(a)). There was severe stenosis of >90% at the start of the left descending branch, while coronary stenosis of about 50% was diffusely observed in the other coronary arteries. Moreover, the entrance of the right coronary artery was deformed due to moderate atherosclerosis on the right aortic sinus (Fig. 1(b)). The left and right lungs weighed 821 g and 974 g, respectively, and there were no significant findings except for severe congestion and severe edema. The cerebrum with stem and cerebellum weighed 1320 g. No atherosclerosis was detected in any of the cerebral arteries, and there was no infected region in the cerebrum, stem or cerebellum. The intima of the aorta showed moderate atherosclerosis. The other organs demonstrated no significant findings with the exception of congestion.

On microscopic examination, coagulation necrosis and contraction band necrosis were diffusely observed in the wall of the bilateral ventricles, but without inflammatory infiltration (Fig. 2(a)). Myocardial fibrosis was widely seen in the wall of the left ventricle. In addition, vacuolar degeneration was diffusely observed in the myocardial cytoplasm. Basophilic granules were diffusely deposited in the myocardium of the left ventricle and interventricular septum, which were stained by Kossa's method, and these were considered to represent calcification (Fig. 2(b) and (c)). In accordance with severe stenosis at the start of the left descending branch, severe atherosclerosis, which was covered by a heterogeneous fibrous cap, was observed; however, no thrombus was detected in the lumen of the coronary arteries. Moreover, both the sinoatrial (SA) node artery and the atrioventricular (AV) node artery showed stenosis of the lumen, which occupied almost 50% of the area (Fig. 2(d)). In the conduction system, fresh hemorrhage was observed in the His' bundle at the top of interventricular septum. Calcification was detected in the conduction system as well as in the ordinary myocardium. In the ovary, hemorrhage in the vacuole was detected, which was considered to be in the post-ovulation phase. The other organs showed no significant findings. Neither alcohol nor drugs were detected in the blood or urine.

2.2. Post-mortem biochemical blood analysis of the cadaver

The examinations of gonadal hormones and other hormones in the post-mortem blood were performed by a licensed laboratory (SRL Corp., Tokyo, Japan); the results are shown in Table 1. The level of testosterone clearly showed a high value, which was as high as the normal range for an adult male. Estradiol, a major element of estrogen, was also elevated to 2–3 times higher than the normal range for an adult female. The levels of both luteinizing hormone and follicle-stimulating hormone were

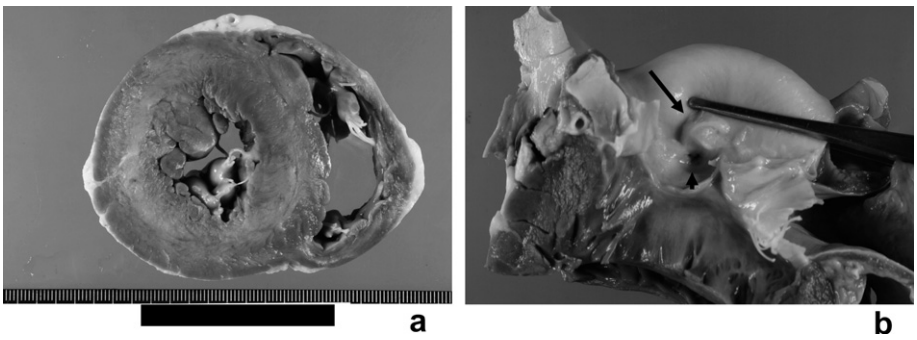

Fig. 1. Macroscopic findings. (a) Concentric myocardial hypertrophy in the left ventricle. (b) Deformation of the entrance of the right coronary artery (black arrowhead) due to moderate atherosclerosis of the right aortic sinus (black arrow).

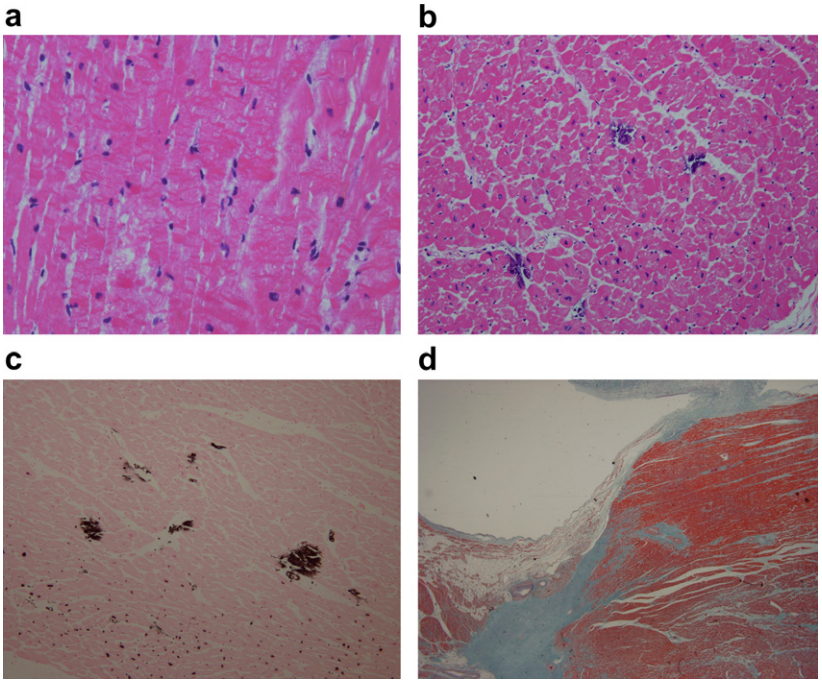

Fig. 2. Microscopic examination of the myocardium. (a) Contraction band necrosis without inflammatory infiltration in the wall of the left ventricle (H.E. stain 200×). (b) and (c) Basophilic granules stained with H.E. in the myocardium of the left ventricle ((b) 100×), which are stained as brown granules with Kossa's method. ((c) 100×). These are considered to represent calcification. (d) Stenosis of the atrioventricular artery (stained with Elastica-Masson 40×).

Table 1
Post-mortem biochemical blood analysis of the cadaver

		Standard value
Testosterone (pg/mL)	12.3	Male: 2.5–11.0; female: 0.1–0.7
Estradiol (ng/mL)	953	Male: 20–59; female: 50–550 (luteal phase)
LH (mIU/mL)	6.32	Male:1.22–7.05; female: 0.90–19.38 (luteal phase)
FSH (mIU/mL)	1.75	Male: 2.00–8.30; female: 1.47–8.49 (luteal phase)
HDL-cholesterol (mg/dL)	28	40–96
LDL-cholersterol (mg/dL)	77	70–139
Total cholesterol (mg/dL)	132	150–219
TG (mg/dL)	111	50–149
t-PA/PAI complex (ng/mL)	<6.0	Male: <15; female: <11

LH, luteinizing hormone; FSH, follicle-stimulating hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein, TG, triglyceride; t-PA, tissue plasminogen activator; PAI, PA inhibitor. Standard values were provided by SRL Co. Ltd. (Tokyo, Japan).

within the standard values at the luteal phase, respectively. High-density lipoprotein (HDL) cholesterol was decreased to below the standard value, whereas low-density lipoprotein (LDL) cholesterol was within the standard value for an adult female.

3. Discussion

There are two methods of therapy for transsexualism, one being sex reversal surgery and the other being cross-sex hormonal treatment.[2–8] Surgical transformation has greater clinical and economic benefits than cross-sex hormonal treatment for transsexual patients.[4,5] On the other hand, cross-sex hormonal treatment for transsexualism has not changed remarkably during the past 30 years, with female-to-male transsexual patients being administered androgen.[3,5–9] In the current case, the cadaver obviously showed virilism, such as hirsutism, acne and strong muscles. On microscopic examination, there were no findings in the ovaries indicative of polycystic ovary syndrome (PCOS), which results in amenorrhea, hirsutism, obesity and polycystic ovaries.[11,12] On endocrinological examination, the level of testosterone slightly exceeded the standard value for a male; however, the level of luteinizing hormone was within the normal range for the luteal phase in a female. Therefore, it was considered that the virilism could be entirely attributed to the administration of testosterone enanthate.

There have been several contraindications to cross-sex hormonal treatment, and there have been several reported adverse effects of the hormonal therapy, including cardiovascular and thromboembolic events in transsexualism patients, but the mortality and morbidity of these has remained controversial.[5–10] From the results of some clini-

cal studies, there has been currently insufficient evidence to exclude adverse effects of exogenous androgen administration in women.[13] However, in animal studies, the development of atherosclerosis in aortic arch was significantly inhibited by administration of testosterone enanthate in castrated male rabbits but not in castrated female rabbits.[14] Additionally, it is reported that hyperandrogenemia in woman, such as PCOS, is associated with visceral obesity, insulin resistance, low HDL-cholesterol, and an increase of triglycerides, LDL-cholesterol, and plasminogen activator inhibitor (PAI), which are considered to be related to cardiovascular disease, whereas exogenous androgen decreases the serum level of HDL-cholesterol, PAI, lipoprotein, insulin and fibrinogen in women as well as in men, which has both beneficial and deleterious effects upon the cardiovascular system.[5,10,13] Recently, there have been several reports stating that testosterone provides protective effects against myocardial infarction in men.[13,15–17] However, Phillips[9] stated that endogenous sex hormones might be related to both atherosclerotic cardiovascular disease and its risk factors in opposite manners in men and women. In the current case, the cadaver macro- and micro-scopically showed no significant findings suggestive of PCOS. Since examination of the cardiovascular system was not performed adequately at the start of cross-sex hormonal treatment, it is actually not known whether the administration of testosterone enanthate directly contributed to atherosclerosis, myocardial fibrosis and myocardial calcification. In particular, it is generally said that myocardial calcification is observed in necrotic tissues or post-necrotic scars (dystrophic calcification), or is due to hypercalcemia (metastatic calcification).[18–20] In the current case, there was stenosis of 50%–90% throughout the coronary arteries; however, there were no significant findings in the parathyroid. Calcification was not seen in organs other than the heart. Thus, it is likely that the myocardial calcification had developed due to chronic ischemia resulting from coronary stenosis. Moreover, coagulation necrosis and contraction band necrosis were seen in the myocardium, which was considered to be due to acute ischemia. In addition, Nishida et al.[21,22] suggested that stenosis of the AV node artery could lead to the development of arrhythmia. Accordingly, we diagnosed the cause of death as ischemic heart disease (IHD) due to coronary stenosis.

There was a report of sudden cardiac death case where anabolic androgen steroids might contribute directly to the development of regional myocardial fibrosis and focal myocardial necrosis, leading to the occurrence of fatal arrhythmia.[23] Moreover, it has been reported that the missense mutation of cardiac ryanodine receptor gene, which encodes the major intracellular Ca^{2+} release channel on the sarcoplasmic reticulum of cardiomyocyte, is related to the development of fatal arrhythmia.[24,25] In the current case, it is possible that myocardial calcification is related to the disorder of handling of Ca^{2+} in the cardiomyocytes. Thus, it is likely that the cause of death of the cadaver is a fatal arrhythmia induced by the other causes in addition to IHD. At any rate, we consider that assessment of cardiovascular function should be performed prior to cross-sex hormonal treatment until the relationship between exogenous androgen and coronary heart disease can be completely refuted on the basis of clinical evidence. Moreover, a periodical inspection of the cardiovascular system should be carried out during cross-sex hormonal treatment, as well as at before the treatment.

In conclusion, we describe an autopsy case of a female-to-male transsexual patient, who was intramuscularly administered testosterone and who died due to IHD. It is possible that, if the physician had performed the appropriate examinations and treatments for the patient, she may not have died due to IHD. Therefore, a physician should examine the cardiovascular system of a transsexual patient before administering cross-sex hormonal treatment, and should periodically examine the cardiovascular system of the patient during the continuation of the therapy. Moreover, physicians should always suspect IHD when a patient complains of chest discomfort, as in the current case.

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